Report of the Committee on the Ethics of Gene Therapy

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Report of the Committee on the Ethics of Gene Therapy

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Foreword

Every significant development in science or technology has been accompanied by dangers both known and unknown. Society watches this progress with mingled admiration and anxiety, the more acute perhaps as science gets ever closer to the fundamental controls over the nature and composition of living things.

To prohibit the progress of science in any particular direction may well be tyranny; to seek to shape its course is surely sensible. In doing so we should be careful also to preserve the right of society to determine how the achievements of science are used.

What we have done in the pages which follow is to suggest some constraints over another remarkable step in our progress towards prevention or relief of some of the sufferings and handicaps of fellow-beings. We have felt strongly the need to protect the liberty of choice in society and to promote the care as well as the cure of the handicapped. That task was made easier by the marked consistency of opinion in the response to consultation.

We should perhaps emphasise that nowhere in our deliberations did we discern the existence of, or the need for, some new ethical principle. Rather we found ourselves considering the application of familiar and established principles to a new and promising field.

Cecil M Clothier KCB QC
10 September 1991

Acknowledgment

We record with gratitude our indebtedness to our excellent Secretariat who have sustained our endeavours and struggled to translate our sometimes tangled thoughts into comprehensible declarations. In particular, we owe a great deal to Dr Ian Lister Cheese and Mrs Sue White.

Committee on the Ethics of Gene Therapy

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1 Introduction

1.1. *Genes* are the essence of life: they carry the coded messages that are stored in every living cell, telling it how to function and multiply and when to do so. Until recently a genetic message could be altered only by accident or chance. Now human ingenuity makes it possible to manipulate these messages deliberately and with increasing precision. Such manipulations might yield significant benefits, especially if they can be applied to the prevention or relief of diseases which have a genetic cause. But they might have unwanted effects. They might, for example, cause harmful or otherwise unacceptable genetic alterations, or lead to social abuses.

1.2. Mindful of the ethical issues raised by the prospect of *gene therapy* being introduced into medical practice, and public concerns that such a development might evoke, the Government established this non-statutory body, the **Committee on the Ethics of Gene Therapy,** in November 1989.

Terms of reference

1.3. Our terms of reference were:—

> "To draw up ethical guidance for the medical profession on treatment of genetic disorders in adults and children by genetic modification of human body cells; to invite and consider proposals from doctors wishing to use such treatment on individual patients; and to provide advice to United Kingdom Health Ministers on scientific and medical developments which bear on the safety and efficacy of human gene modification".

1.4. The Committee reports to the Ministers responsible for health in England, Wales, Scotland and Northern Ireland.

Method of working

1.5. The Committee met for the first time on 30 January 1990 and has met 14 times. We invited written evidence at an early stage in our deliberations. Copies of our letters and published invitation are at Annex A. We received submissions from those who are recorded at Annex B, and are grateful to all of them for their contributions. Others have considered these issues before us. We have scrutinised their reports (Refs 1–8) and have been much helped by them. Members of the Committee were also fortunate in being able to take part in conferences arranged by the Royal College of Physicians of London (Ref 9) and the Royal Society (Ref 10), at which gene therapy was discussed.

1.6. As our discussions progressed we decided that it was proper to examine a number of matters which, although strictly outside our remit, were closely related to it. It might, for example, be more appropriate to treat a *genetic disorder* before the birth of a child who is known to be affected. We felt it was necessary to give consideration to this aspect.

1.7. Our terms of reference specified human *body cells*. This term is normally used to exclude *cells* of the *germ line*, which give rise to sperm or ova *(gametes)* and are responsible for genetic inheritance. There is a belief, which was strongly affirmed in the responses to our consultation, that genetic treatments of human beings should not be undertaken if they are designed to, or may inadvertently, affect future generations. We thought it right to examine this subject too. Lastly, we considered and came to a view on the possible application of gene modification to normal human *traits*.

Background

1.8. Developments in *molecular biology* are progressing rapidly. Our knowledge of genetic material has advanced to the stage where some individual genes have been identified and their structures and functions are coming to be understood. Techniques have been developed which make it possible to isolate particular genes and to transfer them into living tissue where they take on their specific roles. During 1990, in the United States, following a decade of public debate, agreement was reached on the conditions to be observed for a patient to receive gene modification of selected body cells, in an attempt to alleviate and possibly cure a specific genetic disorder (Refs 11,12). This has now been carried out—on a child with a life-threatening inherited disorder characterised by the inability to mount an effective response to infection (Ref 13). There has been a subsequent attempt in Italy also. Such treatment is known as gene therapy.

1.9. Genetic disorders range widely in their effects, from minor discomfort to severe disability and premature death. They are an important cause of prolonged and life-threatening illness, commonly in childhood, and they inflict much distress upon families. Although there are effective treatments for some of these disorders conventional treatments for most of them are inadequate, and for many are limited to the relief of symptoms. Gene therapy offers for the first time in many genetic disorders the prospect of effective treatment and cure.

1.10. Quite apart from necessary questions about the safety of any new medical intervention, it is not at all surprising that there are public concerns about a procedure which could be used to change inherited human characteristics, especially if those changes might be passed to future generations. In addition, there are likely to be irrational fears which derive from misunderstandings of biology, and are compounded by the effects of popular creations of fiction, such as Frankenstein's monster (Ref 14).

1.11. Gene therapy will be a new resource in medical practice and will raise the familiar ethical questions attending any novel form of treatment. But it may also introduce new and possibly far-reaching ethical issues which have not previously had to be considered. It is not merely a fear of the unknown that engenders caution, but also a recognition that the ability to modify the genetic endowment of human beings provides opportunities to influence life and health more fundamentally than could any treatment available hitherto.

1.12. We begin from the presumption that the development of new ways of relieving human distress is to be welcomed, but that they should be used prudently. Before gene therapy is introduced into medical practice it must be ethically acceptable, a requirement of which is that it should stand proper tests of safety and effectiveness in relation to other treatments. We have sought to define the elements of ethical practice in gene therapy and the means for ensuring that they are observed.

1.13. Many who read our report will be unfamiliar with the subject of genetics. The account of our deliberations is therefore preceded by an introductory guide to the subject. It is necessarily brief and for those who wish to read further a selected bibliography is given. Technical terms shown in italics, not all of which are fully explained when they first appear, may be referred to in the Glossary.

2 Genes, Genetic Disorders and Gene Therapy: An introductory guide

Genes and proteins

2.1. The possession of genes distinguishes living things, or organisms, from inorganic matter. The fundamental unit of living things is the cell, and genes are present at some time in every cell. Genes contain the basic coded messages for the structure and functioning of cells, their orderly contribution to the organised growth and repair of *tissues* and *organs*, and to the integrity of the body as a whole; and for procreation. The message coded in each gene is a recipe for making a *polypeptide* which comprises all or part of a particular *protein*. Proteins also are found in every kind of cell, where they are structural components or carry out the many processes which cells undertake.

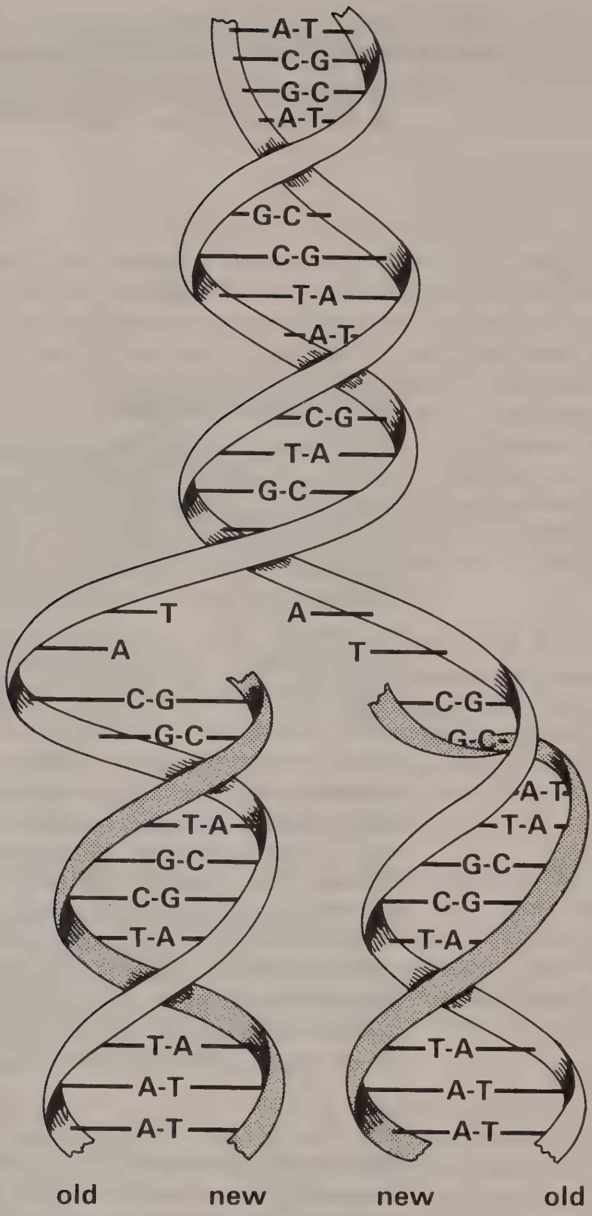
2.2. The great variety of living things is made possible by their rich genetic diversity, which provides an equally rich diversity of proteins. Despite the very large number and variety of proteins they are all constructed from a selection of only 20 distinct compounds called *amino acids*. The different proteins of the body whether, for example, of skin or hair, or of *haemoglobin* which fills red blood cells and takes up and delivers oxygen, or the multitude of other proteins that drive the body's chemical reactions, and produce energy, heat and movement, are all made from a selection of these few amino acids. Proteins differ because in each of them a particular selection of amino acids is assembled in a particular order. Genes specify this arrangement. Each protein, or part of a protein, is constructed according to the coded recipe of its own gene.

2.3. It has been estimated that between 50,000 and 100,000 genes work together to make a human being. Significantly, every kind of body cell contains all of them. Each cell, however, employs only those genes necessary for its own tasks, at any one time using only about a hundredth of the total, the pattern of use varying according to the role assigned to the cell and to fluctuating demands for the manufacture of different proteins. For example, a heart muscle cell uses genes which are different from those used by a liver cell: the heart and liver therefore have correspondingly different structures and functions. Moreover, different genes are brought into play at different times of life. Certain functions of cells of the developing brain of an early embryo, for example, are quite different from those required in the brain of an adult.

DNA

2.4. Genes are made up of a chemical substance called *DNA (deoxyribonucleic acid)*. DNA has two remarkable properties. First, it can make a copy of itself; secondly, it carries the code which specifies every amino acid and its place in a protein.

2.5. An explanation of these properties is to be found in the structure of DNA (Figure). DNA is made of two strands, arranged as a double helix, rather like a twisted rope ladder. Each strand consists of a backbone made from a chemical compound called *deoxyribose*. To this backbone is attached at intervals one of four chemical compounds called *bases* (or *nucleotides*), which are known for short as C, A, T and G. Each base of one DNA strand links with a base of the other



To reproduce itself, the DNA double helix uncoils, the strands separate, and each strand forms a template for its complement, a mirror image of itself. The " rungs " of the DNA helical ladder are made of base pairs, **A** always pairs with **T**, and **C** with **G**. The new DNA double helices are identical to the parent. **A** = adenine, **T** = thymine, **C** = cytosine, **G** = guanine. From Arthur Kornberg, *For the Love of Enzymes* (Cambridge, Mass.: Harvard University Press, 1989), p. 224.

strand according to a simple rule: C links with G, and A with T, thus making as it were the rungs of a ladder. The result of this pairing is that one strand is like a mirror image of the other. If the paired strands are separated their bases are able to link with others floating nearby, observing the same rule. This allows a matching strand of DNA to be assembled alongside each of the two originals, a process known as *replication.*

2.6. Within the paired strands of DNA are specific regions which bear the codes for making proteins, together with codes for controlling when and how much of each protein is made. These regions are the actual genes. The code which DNA carries is surprisingly simple. It uses a chemical alphabet provided by the four bases C, A, T and G. A combination of three successive bases (called a codon) codes each amino acid. The different bases offer 64 possible combinations, more than sufficient to provide a different code for each of the 20 or so amino acids. Permutations of codons along the gene specify the order of amino acids in the corresponding polypeptide which comprises all or part of a protein. The average protein, which contains about 300 amino acids, could be coded by 900 base pairs.

2.7. Paired strands are the form in which DNA is usually present in cells, their bonds serving to stabilise them and to keep them intact. But this matching arrangement has greater significance. Body growth and repair depend on cells increasing their numbers by dividing into two daughter cells, each of which contains the original genetic recipe. Before a cell divides the DNA strands part and, as described above, the mechanism of replication provides a copy of the original double strand for each daughter cell, a process that is repeated as cells multiply.

2.8. The DNA within each cell is folded into compact bundles called *chromosomes*. Chromosomes are present in pairs in the body cells (the *diploid* condition), but only one of each pair is present in sperm or ova (the *haploid* condition). In human beings there are normally 23 pairs, one of every pair having been inherited from each parent. Except for the chromosomes called X and Y, which determine the sex of the individual (two X chromosomes for females, an X and a Y for males), the chromosomes in a pair are very similar. But they are not identical, and their corresponding genes (which are called *alleles*) may differ. These differences, to which the parents make equal contributions, enrich the genetic endowment of the individual. When that individual in turn becomes a parent, half of this endowment is received by offspring. Genes are inherited as parts of a chromosomal package. When sperm or ova are formed they receive only one of each of the paired chromosomes. During the process, which is called *meiosis*, parcels of genes are exchanged between the chromosomes of each pair. So each chromosome within a sperm or ovum contains a new and unique assortment of genes, derived from the corresponding pair of parental chromosomes but different from either. Finally, at fertilisation, when a sperm from the father combines with an ovum from the mother, the fertilised ovum comes to contain a full set of paired chromosomes.

Mutations

2.9. The relationship between the message carried by a gene and the protein it specifies is very precise. An alteration in the gene, which is called a *mutation*, brings about a change in the manufacture of the corresponding protein. There are several possible consequences. The gene might stop working altogether; or the change in the protein and its function might be insignificant; or the mutation might even result in a protein which is more useful. But it might give rise to a protein that has lost its normal function, or one that is harmful. These effects largely account for the consequences of mutations, whether normal variations, or minor defects of the body's working, or, in the extreme, the major genetic disorders. The last occur when a protein that is essential for normal healthy life is absent, or has lost its usual function, or has become harmful. Mutations which are carried in sperm or ova are capable of being passed from generation to generation, according to the rules of genetic inheritance; so too are normal traits, defective ones and the specific disorders for which they are responsible.

Germ line cells and somatic cells

2.10. The many different cells which make up the body are of two kinds:

germ line cells, which during the first few weeks after conception are put aside in the embryonic sex organs to provide ova or sperm; and

somatic cells, commonly called body cells, which include all other cells of the body.

The genes carried by each of these two kinds of cell have distinct roles, and the distinction is very important.

2.11. Genes which are carried by germ line cells may be transmitted to offspring and successive generations. Genes which are carried by somatic cells have their role in the corporate life of those cells within the tissues and organs of the individual whom they endow. So far as is known, an alteration to the genes of somatic cells will affect only that individual, but an alteration to the genes of germ line cells might affect offspring and successive generations.

2.12. A genetic mutation inherited from either parent will necessarily be present in both the germ line and somatic cells. Indeed it is the normal state of affairs that, except when a new mutation arises in the germ line, the genetic endowment of offspring is determined by the genetic endowment of parents, although decided by the rules of chance which govern biological inheritance.

Genetic disorders

2.13. The influences of both genetic and external factors are, to varying degrees, present in all human disorders. Many genetic disorders are the direct consequence of mutations in single genes. Genetic disorders also result from defects in whole chromosomes (as in *Down's Syndrome*); or from the interactions of multiple genes and external factors early in fetal development which are the cause of *malformations* present at birth. Later in life other interactions between multiple genes and external factors seem to be the basis of many of the common serious diseases, including heart disease, diabetes and cancer. More is becoming known about the underlying mechanisms of most of these disorders. Among the most familiar disorders caused by single gene defects are *cystic fibrosis*, *Duchenne muscular dystrophy*, *haemophilia*, *Huntington's disease*, the *thalassaemias* and *sickle cell disease*, and conditions as relatively minor as colour-blindness. Several thousand single gene disorders have been described, most of them rare. Many result in serious illness and death in childhood causing families much distress. There are effective treatments for a number of genetic disorders; nonetheless, conventional treatments are often inadequate and are sometimes burdensome. Treatment and care may be prolonged and costly, both to individuals and society (Ref 15). For example, in one major study of 351 single gene disorders the effects of available treatments were assessed with reference to three outcomes: life span, reproductive capacity and ability to live a normal social life. Treatment produced a normal lifespan in 15 per cent, allowed reproduction in 11 per cent and social adaptation in only six per cent of those affected (Ref 16).

2.14. The prospect of gene therapy is obviously attractive if it can make good the genetic defects responsible, and thereby cure or alleviate disorders in which the outcomes are so dismal. Moreover, the effective introduction of gene therapy into medical practice would also serve to augment and enhance the choices that may face parents who are at high risk of transmitting a serious genetic disorder to their children.

2.15. Gene therapy has wider possibilities for medical practice than the correction of single gene disorders. For example, it is being investigated as a possible new approach to the management of a wide spectrum of diseases, ranging from infections such as AIDS to cancer, and it is being studied as a means of strengthening the body's immune response to viral infections. Various approaches are being used which require the insertion of genes into particular cell populations in an attempt to counter some of the basic changes in cells which lead to them becoming cancerous. Gene therapy is also being explored for the management of chronic diseases such as diabetes. The requirements for demonstration of the effectiveness of this approach in animal systems, and the clear demonstration of its safety, will follow the same principles as those set out for the use of gene therapy to correct single gene disorders.

Normal human characteristics

2.16. Normal variations in human characteristics such as personality, intelligence and physique may also be explained by the inheritance of multiple genes and their interaction, together with environmental influences. We are alert to the profound ethical issues that would arise were the aim of gene modification ever to be directed to the enhancement of normal human traits.

Gene therapy

2.17. Some genes have been isolated, together with the associated DNA sequences which are required to regulate their working in the cell. They have been replicated and their structures and functions studied. Such isolated genes have been inserted into living cells cultivated in the laboratory, which then produce the protein for which the inserted gene carries the code (ie the gene is *expressed*). Isolated genes have also been inserted experimentally into animals and shown to work. This has been applied for practical purposes; for example, human genes have been used in sheep to achieve production of the protein needed to treat haemophilia. It is now possible to insert appropriate human genes into selected cells of patients with specific genetic disorders. These developments have opened the way to gene therapy.

Scientific requirements for gene therapy

2.18. If gene therapy of a particular disorder is to be achieved a number of requirements must be met:

(a) The gene must have been isolated and be available for therapeutic use.

(b) Something must be known of the function of the gene, so that treatment can be sensibly designed.

(c) It must be known which tissues and cell types need to express the gene and when, during development, its expression is required.

(d) The genetic sequences that control the function of the gene, for example by switching it on and off, must be known and have been isolated. If gene therapy is to work it is clearly important that the product of the gene is made in the right cells, in the right amounts and at the right time. Too much or too little of the gene product, or its production in the wrong cells, or at the wrong time during development, could be harmful.

(e) There must be means available for getting the gene, and its controlling elements, into the right cells and under the right control. Conversely, the gene must be prevented from getting into the wrong cells, or to the wrong place within a cell, or from spreading to other tissues, or even to other individuals, any of which might cause harm.

(f) Means must be available for monitoring the efficacy and safety of the treatment, for a long time.

These requirements are discussed in more detail in the following paragraphs.

2.19. As we have said, genes contain the recipes that cells use to make particular proteins. It is obviously important that the genetic recipe should be correct, so that the right protein is made; and just as important that the gene should be expressed at the right time. There are elaborate genetic signals, not yet well understood, which regulate whether particular genes are switched on or off at particular times of development and in particular cells or tissues. This "gene control" must be satisfactorily preserved if a transplanted gene is to work effectively.

2.20. For a transferred gene to do any good it must clearly be targeted into the cells which need it. If a particular gene is essential for the proper function of the liver there is little point in placing it into the hair root cells. It is necessary, therefore, to know in which tissues the gene is required and how to ensure that it gets there.

2.21. Gene therapy could be attempted by seeking to correct part of an abnormal gene to make it functional again; or by removing the abnormal gene and replacing it with a normal one; or by simply inserting a normal gene, so that the necessary gene product is made, while leaving the abnormal gene in place within the cells. At this very early stage of gene therapy research, the last of these approaches, although the least elegant, is likely to be the most practicable, because the technical means for inserting genes into cells are already at hand whereas the means for removing existing genes from cells are much less advanced.

2.22. The inserted gene must be integrated somewhere within the cells being treated, in such a way that it becomes part of the genetic constitution of those cells and is transmitted to the cellular progeny each time the cells divide. Ideally it should be inserted precisely in place of the abnormal gene, and be subject to the same cellular environment and cellular controls as in the natural state. In practice this may be very difficult to achieve, current methods merely allowing the gene to be inserted at any random site within the genetic material of the cell. The majority of genes apparently function satisfactorily following insertion in this way. There is, however, the danger that such random insertion may lead to inappropriate control of the gene—of where, when and how much of the gene product is expressed. It is also possible that the random insertion may actually disrupt some other genetic function, with unwanted consequences.

2.23. Even within a single tissue there are many different types of cell. For example, in blood there are red blood cells and many different kinds of white blood cell. Normally these cells undergo constant replacement and renewal. This biological maintenance programme depends upon the presence of a very small number of *stem cells* whose function it is to generate new cells. If genes are placed in cells other than stem cells their effect will last only for as long as those treated cells survive. As they are replaced the effect of gene therapy will be lost. To avoid this it is necessary to target gene therapy at the stem cells, so that the new cells being formed have the correcting gene in place. This is made difficult because stem cells are few and in many tissues they cannot be easily identified.

Somatic cell gene therapy

2.24. Making good a defective gene in the body cells where it is needed is known as somatic cell gene therapy. The aim is to provide the right genetic information, under proper control, in precisely those cells which need it for their normal function. Ideally the effect should be permanent so that no further therapy is required. It should also be permanent in the sense that the inserted gene is securely lodged. If successful, therapy would make good the genetic defect in the treated cells and tissues of the individual, although the abnormal gene would still be present in other tissues. This is unlikely to matter provided the abnormal gene product has no effect, or, if it is actually harmful, is not used. However, the germ cells, which give rise to sperm or ova, would retain the defective form of the gene, with the possibility of its transmission to future generations.

Methods of gene therapy

2.25. Our interest in the methods available for inserting genes into living cells turns on their safety and effectiveness. Genes can be inserted into cells directly by physical techniques or by using a biological vehicle for delivery. At present, delivery employing suitably modified viruses seems most promising. Viruses are fashioned by nature to enter cells and to insert their own genetic material. Some viruses can be modified to carry genetic material different from their own, and insert it into host cells, and thus provide a technique for gene modification therapy. So far it has been possible only to supplement a defective gene, not to replace it; neither is it yet possible to lodge a gene precisely where it would naturally be. Nonetheless, this approach may well be effective in selected disorders. In time it may be feasible to harness the natural process of *recombination* which allows formation of new combinations of genes.

Germ line gene therapy

2.26. In order to remove the threat to future generations of a defective gene it would be necessary to correct the defect in the germ cells, which give rise to ova and sperm. This is known as germ line gene therapy. Because little is known about the possible consequences and hazards, and any harm to future generations would take a long time to discover and deal with, this application of gene therapy needs to be considered quite separately from somatic cell gene therapy.

Possible dangers of gene therapy

2.27. Among the possible dangers of gene therapy are, therefore, that:

(a) It might not work, in which case the patient will have undergone the procedure without benefit.

(b) The correcting gene might be inserted into the wrong cell type, or be expressed inappropriately, either in the wrong amount or at the wrong time during development. The therapy might then do more harm than good.

(c) The gene might be inserted in such a way as to cause a new mutation, by disrupting some other gene or its means of control. This might initiate a new genetic disease, or perhaps an uncontrolled multiplication of cells which could lead to cancer.

(d) If the means of inserting the gene were faulty, it is conceivable, although in the present state of knowledge improbable, that the gene, or parts of if, might emerge from the cells and be " infective ", moving to other somatic cells or germ line cells, or even to other individuals. This might cause harm to the treated patient and to others.

These factors which bear on the effectiveness and safety of gene therapy must all be taken carefully into account when proposals for gene therapy are considered (Ref 3).

3 Ethical Basis

Introduction

3.1. We begin from the basis that ethics are the moral convictions of thoughtful, conscientious and informed people, to be rejected only when they are in conflict with other convictions which stand better the test of reflection. These convictions are in general derived from a compound of natural philosophy and religion. As statements of principle they are intuitive; the rules and duties derived from them are wrought by moral reasoning. From utilitarian principles, those based on assessments of benefit and harm to individuals and to society, rules and duties are similarly derived. We are alert to the tensions that characterise ethical matters. Given a practical remit we have the task and duty to use such tensions creatively. We cannot, nor should we hope to, remove them.

3.2. Some of the intuitive convictions we have in mind are reverence for life and respect for the dignity and integrity of the person; the right to freedom and, especially in our context, a freedom of choice based on the right to knowledge; respect for privacy and the preservation of confidences; the importance in society of fairness and equity; and, casting its light over all, the quest for truth. Our subject, genetics, requires us to consider the implications of gene therapy for both present and future generations. We may speculate upon, but cannot confidently predict, attitudes which may come to be held in future. Meanwhile we believe that close attention must be given to the detail of what, in gene therapy, is feasible and might be proposed, its purposes, and the possible consequences, whether intended or inadvertent.

3.3. To find an ethical position which would command acceptance in this country for the foreseeable future we have consulted widely among individuals and bodies representing diverse religious and cultural beliefs. We have also taken careful notice of the treatment of these matters in other countries of similar cultural heritage. Unsurprisingly, the same questions have been discussed elsewhere, and with a consistency in approach and underlying ethical conviction which have made our task easier.

3.4. The first ethical principle which has commanded our attention is the obligation inherent in human nature to enquire, to study, to pursue and apply research by ethical means.

3.5. The possibility of human benefit is conjoined with the possibility of contingent or inadvertent harm. The harm may be to individuals, arising, for example, from the unforeseen consequences of a genetic manipulation. Or the harm may be to the community, by a breach of values widely held. Or, in the context of medical practice, it may threaten the trust in which resides the strength of relationships between doctors and their patients.

3.6. The second ethical principle which has governed the deliberations of the Committee is that in the sometimes inescapable tensions between the pursuit of knowledge and the protection of patient's interests, the latter must prevail.

3.7. The expression of these principles, and the tension between them to which we have alluded, will become explicit when we consider the details of what, in the field of therapy by gene manipulation, may be proposed and what is ethically permitted.

Ethics of medical practice and medical research

3.8. Different codes of practice and means of regulation have evolved to govern medical practice, innovative treatment and clinical research involving patients (Refs 17–21). However, the distinctions between these activities are not always clear, a matter which has provoked much concern (Ref 22). The Royal College of Physicians of London, in two documents, "*Guidelines on the practice of ethics committees in medical research involving patients*" (Ref 18) and "*Research involving patients*" (Ref 19) has addressed the issue. It finds that the distinction derives from the intent and in the second document states:

> "Where an activity is undertaken solely with the intention of benefiting an individual patient, and where there is a reasonable chance of success, the activity may be considered to be part of 'medical practice'. The progressive modification of methods of investigation and treatment in the light of experience is a normal feature of medical practice and is not to be considered as research.
>
> In contrast, where an activity involving a patient is undertaken with the prime purpose of testing a hypothesis and permitting conclusions to be drawn in the hope of contributing to general knowledge, this is 'research'. The fact that some benefit, expected or unexpected, may result from the activity does not alter its status as research.
>
> The distinction between 'medical practice' and 'research' is often less clear than is suggested above because both are practised simultaneously. Sometimes special circumstances of an individual patient's illness lead a clinician to step outside what is accepted as normal medical practice. We distinguish between innovative treatment of this sort and research.
>
> In innovative treatment, the sole motive for the action is to choose the best possible course of action for the individual patient, even though it be unconventional. It remains innovative treatment rather than research even if, as a by-product, useful information is gained. Responsibility for employing innovative treatment remains that of the clinician, who remains subject to the usual constraints which direct ordinary medical practice.
>
> Where a clinician contemplates a marked digression from normal medical practice in an individual case, with the prime purpose of acquisition of information for application in future patients, the activity clearly becomes research and must be subject to all the considerations of proper consent and scrutiny by Research Ethics Committees which are described in this report". (Op cit 2.2–2.7).

Gene therapy: Innovative practice or research?

3.9. The initial use of gene therapy will clearly be a digression of this sort from ordinary medical practice. Indeed, the establishment of this Committee acknowledged concerns that gene therapy is perceived as different, both in its nature and possible consequences, from treatments used hitherto in medical practice, including those already applied to the treatment of genetic disorders. The prospect has raised the question whether gene therapy should be subject to more than the usual constraints which direct ordinary medical practice and innovation, or even those which at present govern medical research.

3.10. Our discussions and enquiries confirmed our tentative view that, notwithstanding the primary intention to benefit an individual patient, gene therapy should initially be regarded as research involving human subjects, and governed by requirements at least as exacting as those which at present applied to that kind of research. Accordingly, any proposal to conduct gene therapy should be subject to approval following authoritative ethical review, which includes critical scrutiny of its medical and scientific merit, the legal implications, and wider public concerns. It should also be subject to conditions laid down for the conduct and oversight of therapy and evaluation and reporting of the outcome. In what follows we consider the detailed basis of this view and the means by which it may be given force. This position is in keeping with the general view that any marked change in medical practice should be subject to the discipline of scientific, medical and ethical appraisal before its introduction.

Ethical basis of research on human subjects

3.11. It is generally agreed that research on human subjects should conform with accepted ethical codes and that investigators should not be the sole judge that their researches so conform (Ref 20). The purposes of such ethical codes, together with the means of giving them force, are to:

(a) facilitate justifiable advancement of biomedical knowledge;
(b) maintain ethical standards of practice;
(c) protect the subjects of research from harm;
(d) preserve subjects' rights and liberties; and
(e) provide reassurance to the public, to the professions and to Parliament that these are being done.

3.12. In the following chapters we apply these ethical codes, and the principles on which they are founded, to gene therapy. We consider what in gene therapy research is justifiable, and the conditions that should be met for such research to be ethical and seen to be so.

3.13. In Chapter 4, **Somatic cell gene therapy,** and in Chapter 5, **Germ line therapy,** we give particular attention to those aspects of gene therapy which heighten familiar ethical concerns or raise new ones.

4 Somatic Cell Gene Therapy

Purpose of somatic cell gene therapy

4.1. The purpose of somatic cell gene therapy in an individual patient is to alleviate disease in that individual, and that individual alone. There would be no intention to modify the gene in the germ line. We consider that the development of safe and effective means of gene modification for this purpose is a proper goal for medical science, and we **recommend** that the necessary research should continue.

Initial application of somatic cell gene therapy

4.2. A new treatment yet unproven in human subjects should only be contemplated when the potential benefits outweigh possible harm, including inadvertent harm, to the patient, and to others, and any discomfort and distress that might accompany treatment. It is evident that this position is now being reached in respect of gene therapy for a number of serious genetic disorders. Somatic cell gene therapy may hold great potential benefit for some patients, but it may also carry risks which are more than minimal. Therefore, to ensure that the benefits are assessed and the risks are identified as expeditiously as possible, we **recommend** that somatic cell gene therapy should, for the present, be conducted according to the discipline of research.

4.3. The first candidates for gene therapy should be patients who are suffering from a disorder which is life-threatening, or causes serious handicap, and for which treatment is unavailable or unsatisfactory; but which has not already progressed so far as to reduce significantly the potential for benefit. Therapy should hold promise of bringing about a remission in the advance of the disorder whilst sparing the patient any unduly adverse consequences of treatment. To achieve most benefit, by preventing suffering, impaired development and irreversible damage, gene therapy should be considered at the earliest possible stage in the course of the disorder. A patient who had already suffered irreversible tissue and organ damage would be subject at best to only partial relief by gene therapy. Among those disorders to which gene therapy might be applicable are some which lead to irreversible and cumulative effects from early childhood, and even before birth. In such instances therapy must be given correspondingly early in life.

4.4 The basic structures and organs of the body are formed during the first few weeks after fertilisation. If, because of a genetic defect (or, indeed, any other adverse influence), this early development has been impaired it is unlikely that any resulting structural fault could be corrected except by surgery. This state of affairs naturally leads to the consideration of interventions that might be possible in the very earliest stages of life, soon after fertilisation. There are many technical problems to be overcome, and there would need to be clear safeguards for the mother; but we see no objection in principle to such a procedure provided it takes place after differentiation of the germ line cells, which has occurred by five weeks after fertilisation (Ref 23). (See Chapter 5).

Somatic cell gene therapy research

4.5. The normal rules which govern research in human subjects and the requirements for prior ethical review and approval of research and its subsequent oversight, which have been considered in Chapter 3, should apply to somatic cell gene therapy. When a patient who is the subject of such research stands to benefit directly from participation it is properly described as therapeutic research.

4.6. A decision on whether gene therapy research should proceed must depend on the careful prior assessment of the balance of potential benefits and risks for the individual patient. This assessment must draw on knowledge of the genetic basis of the disorder, its pathological effects and clinical course. It will call for evidence of adequate experience of gene modification in experimental systems using isolated cells and laboratory animals, and must incorporate a judgement on the possible consequences of the proposed treatment. The risks to the patient will largely depend on the safety of procedures for introducing genes into cells therapeutically, and the effects, both immediately and in the long term. Safety must be a foremost consideration when proposals to conduct gene therapy are made. Intrusions on privacy, too, are an inevitable accompaniment of such pioneering procedures and the long term follow-up that is necessary.

4.7. In their joint statement the European Medical Research Councils (Ref 3) brought out clearly the technical complexity of the procedures used in gene modification. Undesirable consequences (to which we have drawn attention in Chapter 2) might include genetic modification of the germ line, and its effects in progeny; modification of somatic cells other than those which have been targeted; interference with the normal working of modified cells; cancerous changes in cells of the population modified; and changes induced by the insertion process.

4.8. The crucial first step in ethical review is a careful assessment of the scientific merits of the proposal, the competence of those wishing to carry out gene therapy, and the potential benefits and risks in each particular instance for which a proposal is made. This assessment should include a critical examination of the arrangements to be made for the conduct of therapy and subsequent monitoring. It will necessarily call upon an uncommon degree and range of scientific and medical expertise, encompassing a deep knowledge of molecular biology, of experimental work in gene manipulation, and close familiarity with the molecular basis and clinical features of the disorder under consideration. No existing body is constituted for these tasks. Accordingly we **recommend** that a supervisory body with the necessary collective expertise, experience and authority be set up, having the responsibility for making such assessments in conjunction with ethical review. We also **recommend** that any proposal for gene therapy must be approved by this body as well as by a properly constituted local research ethics committee (LREC) (Ref 20). (See Chapter 6).

4.9. There is a duty to identify and assess promptly any adverse consequence of gene therapy for the patient, both in the aftermath of treatment and in the long term. This duty does not end with the death of the patient. To verify that therapy has not inadvertently affected offspring and successive generations monitoring should extend at least into the next generation. Indeed, insofar as it is possible, monitoring should continue over several generations. Therefore, those conducting such research have a duty not only to maintain adequate records but also to ensure that an effective monitoring system is in place. It will require that a register be set up, and carefully maintained, with safeguards to protect confidentiality. We **recommend** that the necessary arrangements are made before the therapy begins. A complementary duty is to obtain the reliable commitment of patients, and their families, to participate in extended follow-up. During the process of informing and counselling, and obtaining consent, the patient should learn of the need for such follow-up and understand the reasons for it. The patient should also be made aware that although follow-up might be intrusive and burdensome the doctors accept a duty to minimise these effects.

4.10. Accordingly, the conditions which must be satisfied when gene therapy research is proposed are that:

(a) There must be sufficient scientific and medical knowledge, together with knowledge of those proposing to undertake the research, to make sound judgements on:
   - (i) the scientific merit of the research;
   - (ii) its probable efficacy and safety;
   - (iii) the competence of those who wish to undertake the research; and
   - (iv) the requirements for effective monitoring.

(b) The clinical course of the disorder must be known sufficiently well for the investigators and those entrusted with counselling to:
   - (i) give accurate information and advice; and
   - (ii) assess the outcomes of therapy.

Consent to research

4.11. A prior ethical requirement of research involving patients is the consent of the individual subject. Consent implies that sufficient information has been given, in a form that is understood, to enable that individual to make a voluntary decision to participate or not. Because gene therapy has novel, complex and possibly far-reaching aspects we are concerned to ensure that the patient is enabled to take these fully into account when giving consent. It is important that serious attention be given not only to the content of the information given to the patient but also to the way in which it is conveyed. Above all, care must be taken to ensure that the patient has understood the risks, benefits and obligations, and has the fullest possible information. Independent advice, not aimed at obtaining consent, should ideally be provided by someone unconnected with the research or therapeutic team and well versed in the implications of gene therapy.

4.12. We foresee the possibility that a competent adult, in whom the disorder had progressed to a stage at which there was little prospect of direct benefit from therapy, might nevertheless consent to participate in non-therapeutic research—for the collective human benefit that the research should be designed to yield. For such research to be ethical it must be possible to assess the consequences of the procedure, by measurement or detection of changes within the body, or their absence, even if there were to be no discernible clinical benefit. We conclude that participation by a competent adult in such research is acceptable.

4.13. Children with genetic diseases are likely to be among the first candidates for gene therapy. The special problems to be faced when children are the subjects of research have been examined in existing guidelines (Refs 17–22, 27). The foremost consideration must be the best interests of the child, and in this respect somatic cell gene therapy raises no new ethical issue.

Confidentiality of genetic information

4.14. Clear principles govern the confidentiality of personal health information obtained within the National Health Service (NHS), the use of such information, and the circumstances in which it might be disclosed. They are set out in guidance *"Confidentiality, Use and Disclosure of NHS Information"* (Ref 24) which is to be issued shortly. This guidance takes account of the ethical obligations of health professionals towards protecting the confidentiality of personal health information.

4.15. The duty of confidentiality is by no means absolute; it is balanced by a duty of disclosure. The tension is heightened when the special qualities of genes and genetic events give rise to different, and possibly conflicting, interests of kindred, including those yet unborn, who share, or might share, the same genes. For example, an individual might be the source of genetic information which is important to relatives. It might be important to their health care, decisions on parenthood, or life plans which might be influenced by known health risks. Conversely, information which is important to a particular individual might only be obtainable from relatives. These factors have a bearing on the confidentiality of such information and the circumstances in which it might be disclosed. Similar considerations also lead to the question of just what genetic information should be sought from any individual. These issues are already familiar to clinical geneticists, who are guided in their practice by evolving codes on the circumstances in which the boundaries of confidentiality may be extended beyond the individual to include kindred. Therefore, when consent to treatment is sought, which in the case of a child will be from the parents or guardians or other persons who may legally be in a position to give consent on behalf of the child, the possible need for subsequent disclosure of personal health information should be discussed.

4.16. In the case of a child, the parents or others giving consent should first be told that the duty of confidentiality is to the child and, whatever their wishes, that it is in the child's best interests, at the proper time, to know its own clinical history. There might also be a duty, as stated above, to disclose the information to others, including those of subsequent generations.

Gene therapy and the essence of humanity

4.17. The total complement of genes which are found in the human population, the human *gene pool*, is the source of human genetic variability. From it is drawn the parental contribution to the unique endowment of genes possessed by each individual human being, or by identical twins. The interaction of these genes and external influences throughout life confers the quality of humanness, a quality that in each individual is characterised, in part, by variants which determine human differences, and contributes to the collective quality we call humanity.

4.18. This is the background against which we have considered the origin of material that might be used in gene therapy. So far as we can see the genes used in therapy will come from a human source. Should it ever become clinically necessary to use genes which have been derived from any species other than man we believe that such use would in no way impair the humanness of an individual who received the gene. The change conferred would be no different in kind from that resulting from any medical intervention which introduced tissue from other individuals; for example, an organ transplantation, or blood transfusion; or, indeed, from another species, as in the case of pig's heart valves, which are commonly used to replace defective valves in the human heart.

Preclinical experimental procedures

4.19. We are sensitive to issues raised by the use of laboratory animals in genetic experiments that precede therapy in patients. These issues are common to all experimentation in animals. They concern the welfare of such animals, which is a responsibility of the Home Office. However, the types of procedures used in preclinical genetic studies raise no new problems either in substance or scale.

4.20. The safety of procedures for gene manipulation is a responsibility of the Advisory Committee on Gene Manipulation (ACGM). ACGM was established in 1984 by the Health and Safety Commission and is primarily responsible for advising on health and safety at work issues, for which the Health and Safety Commission is responsible to the Secretary of State for Employment. ACGM is also able to advise the Health, Agriculture, Environment, Industry and Northern Ireland Ministers on such other matters relating to genetic manipulation as may be referred by those Ministers, and to offer comment on the technical or scientific aspects of any new developments in genetic manipulation which may have implications for their departments. We do not foresee any new problems in this respect but, nevertheless, we **recommend** that the attention of ACGM be drawn to our report.

Costs

4.21. We are not charged with concern for the allocation of national resources as between different kinds of illness, groups of patients, or particular therapies. These are political questions, and the priorities, when resources are limited, must be decided by those entrusted with the provision of health care, guided by the national will as expressed through Parliament. We do, however, draw attention to the high costs of treatment and care of patients who are afflicted with chronic disorders of genetic origin which are severely disabling (Ref 15). These financial and human costs are not borne by health services alone, but also by other agencies, and by families themselves. In the event of the potential benefits of gene therapy being realised, these costs should be set against the costs of therapy and the provision of services and access to them, and savings that alleviation of these diseases may bring.

Limits to somatic cell gene therapy

4.22. We are firmly of the opinion that gene therapy should at present be directed to alleviating disease in individual patients, although wider applications may soon call for attention (see 2.15). In the current state of knowledge it would not be acceptable to use gene modification to attempt to change human traits not associated with disease. In addition, whilst we recognise that many selective influences, whether random, accidental, or caused by medical interventions, result in changes to the total human gene pool, we hold the general view that human genetic variability and diversity are precious and should be protected.

Conclusion

4.23. We conclude that the development and introduction of safe and effective means of somatic cell gene modification, directed to alleviating disease in individual patients, is a proper goal for medical science. Somatic cell gene therapy should be regarded, at first, as research involving human subjects and we **recommend** that its use be conditional upon satisfactory scientific, medical and ethical review. Although the prospect of this new therapy heightens the familiar ethical concerns which attend the introduction of any new treatment, we conclude that it poses no new ethical problems. However, in view of the scientific and medical complexity of this treatment and the need for a most careful assessment of the therapy proposed in each instance, and subsequent long term monitoring, we **recommend** that a new supervisory body should be set up and charged with these tasks.

5 Germ Line Gene Therapy

5.1. The purpose of gene modification of sperm or ova or cells which produce them would be to prevent the transmission of defective genes to subsequent generations. Gene modification at an early stage of embryonic development, before differentiation of the germ line, might be a way of correcting gene defects in both the germ line and somatic cells. However, we share the view of others that there is at present insufficient knowledge to evaluate the risks to future generations, to which we have already pointed.

5.2. We **recommend,** therefore, that gene modification of the germ line should not yet be attempted. For couples identified as being at risk of bearing a child with a serious genetic disorder, embryonic diagnosis and selective implantation of an unaffected embryo would provide another way of achieving the same end without incurring the unknown risks of germ line modification (Ref 25). (See 4.3–4.4). Moreover, this approach offers the prospect of avoiding genetic disorders which result in structural fetal abnormalities.

6 Supervision of Gene Therapy

Expert Supervisory Body

6.1. Among our tasks were: to invite and consider proposals from doctors wishing to use such treatment on individual patients; and to provide advice to United Kingdom Health Ministers on scientific and medical developments which bear on the safety and efficacy of human gene modification. An assessment of the safety and efficacy of gene therapy, and of the design, content and conduct of research involving patients, depends upon technical, scientific and medical expertise which only a minority of members of this Committee possess. Similar expertise is required in this field to provide advice to Ministers. During consultation we encountered much support for the setting up of a new expert group. Local research ethics committees (LRECs), in particular, wished for a national body to which they could look for advice when proposals to conduct gene therapy research were submitted to them for ethical review. Moreover, we have come to the conclusion that continuing supervision of gene therapy is necessary. No existing body is constituted for these tasks. Consideration of particular proposals for research is excluded from the tasks envisaged for the Nuffield Bioethics Council which was set up during 1991. Therefore, to discharge the second part of our remit, we **recommend** the establishment of a new expert supervisory body [4.8].

6.2. We **recommend** that this supervisory body should be of sufficient standing to command the confidence of LRECs, and of the public, the professions and of Parliament. It should have a responsibility for:

(1) advising on the content of proposals, including the details of protocols, for therapeutic research in somatic cell gene modification;

(2) advising on the design and conduct of the research;

(3) advising on the facilities and service arrangements necessary for the proper conduct of the research;

(4) advising on the arrangements necessary for the long term surveillance and follow-up of treated patients;

(5) receiving proposals from doctors who wish to conduct gene therapy in individual patients and making an assessment of:

  (a) the clinical status of the patient;

  (b) the scientific quality of the proposal, with particular regard to the technical competence and scientific requirements for achieving therapy effectively and safely;

  (c) whether the clinical course of the particular disorder is known sufficiently well

  —for sound information, counselling and advice to be given to the patient (or those acting on behalf of the patient)

  —for the outcomes of therapy to be assessable;

  (d) the potential benefits and risks for the patient of what is proposed;

  (e) the ethical acceptability of the proposal.

In the light of this assessment the expert supervisory body should make a recommendation on whether the proposal should be approved, and if so on what, if any, conditions. The supervisory body should also have a responsibility for:

(6) acting in co-ordination with LRECs;

(7) acting as a repository of up-to-date information on research in gene therapy internationally;

(8) setting up and maintaining a confidential register of patients who have been the subjects of gene therapy;

(9) oversight and monitoring of the research;

(10) providing advice to Health Ministers in the United Kingdom, on scientific and medical developments which bear on the safety and efficacy of human gene modification.

6.3. We **recommend** that any proposal for gene therapy must be approved by this body as well as by a properly constituted LREC.

6.4. Decisions on a therapeutic intervention for an individual should be made promptly, and the new arrangements should not cause unnecessary delay to the consideration of proposals. Therefore, we **recommend** that anyone wishing to conduct such research should submit proposals simultaneously to LRECs and the new supervisory body.

7 Recommendations

7.1. We have concluded that the development of safe and effective means of gene modification, for the purpose of alleviating disease in individual patients, is a proper goal for medical science. We therefore **recommend** that the necessary research should continue [4.1].

Germ line gene therapy

7.2. We are clear that there is at present insufficient knowledge to evaluate the risks to future generations of gene modification of the germ line. We therefore **recommend** that gene modification of the human germ line should not yet be attempted [5.1, 5.2].

Somatic cell gene therapy

7.3. Somatic cell gene therapy will be a new kind of treatment, but it does not represent a major departure from established medical practice; nor does it, in our view, pose new ethical challenges. It will, of course, raise familiar issues which attend any new medical procedure. However, there are public concerns about a medical intervention which may be perceived, understandably, as different from any used hitherto. In addition, because of the special qualities of an individual's genetic make-up and the complex nature of genetic disorders, the issues will assume greater prominence. They are:

(a) questions of safety which are heightened by the possibility of inadvertent and unpredictable consequences of gene therapy to the patient, and the possible long term consequences [4.6, 4.7];

(b) the need for long term surveillance and follow-up [4.9];

(c) the matter of consent, especially in view of (a) above [4.11–4.13];

(d) the probability that children will be among the first candidates for therapy [4.13];

(e) confidentiality, and disclosure of genetic information important to kindred [4.14–4.16].

It is essential to ensure that these issues are properly considered, and to demonstrate satisfactorily that this has been done. We therefore **recommend** that initially somatic cell gene therapy should be governed by the exacting requirements which already apply in the United Kingdom to other research involving human subjects [4.2, 4.5–4.16].

7.4. While the safety and effectiveness of somatic cell gene therapy remain uncertain, this new treatment should, as with any other treatment, be limited to patients in whom the potential for benefit is greatest in relation to possible inadvertent harm. We therefore **recommend** that the first candidates for gene therapy should be patients in whom the disorder is:

(a) life threatening or causes serious handicap; and

(b) for which treatment is at present unavailable or is unsatisfactory [4.3].

Limits to somatic cell gene therapy

7.5. We are firmly of the opinion that gene therapy should be directed to alleviating disease in individual patients, although wider applications may soon call for attention. In the present state of knowledge any attempt by gene modification to change human traits not associated with disease would not be acceptable [4.22].

Expert supervisory body

7.6. In addition, we **recommend** that a new expert supervisory body be established to provide scientific and medical advice on matters germane to the safety and efficacy of human gene modification, and its use. The basis for this recommendation and the proposed remit of the new body are set out in Chapter 6.

Local research ethics committees

7.7. The mechanisms established in the United Kingdom for ethical review, by local research ethics committees (LRECs), of proposals for research involving human subjects, are designed to provide the necessary safeguards to:

(a) facilitate ethical research and the benefits to society that it brings;

(b) maintain ethical standards of practice in research;

(c) protect the subjects of research from harm;

(d) preserve the rights of subjects; and

(e) provide assurance to the public, professions and Parliament that these safeguards are in place.

Any proposal to conduct gene therapy research should, therefore, be subject to ethical review by LRECs. We **recommend** that their approval should be conditional on the approval of the proposed supervisory body [6.3].

7.8. Decisions on a therapeutic intervention for an individual must be made quickly. We **recommend** that arrangements for the working of the proposed advisory body and its co-ordination with LRECs should be made accordingly [6.4].

Advisory Committee on Gene Manipulation

7.9. We **recommend** that the attention of the Advisory Committee on Gene Manipulation (ACGM) be drawn to our report [4.20].

Control and discipline

7.10. We **recommend** that there should be an effective means of control and discipline. If it comes to the attention of a LREC that research is being carried out which it has not been asked to consider or which it has considered but its recommendations have been ignored, then the LREC should bring the matter to the attention of its appointing authority, the relevant NHS body and to the appropriate professional body (Refs 20, 26); the supervisory body should bring it to the attention of Ministers.

7.11. The arrangements that we recommend are, we submit, adequate to provide the safeguards necessary to ensure good practice when proposals to conduct gene therapy are made. They should also be flexible enough to adapt to foreseeable changes in research and clinical practice in the field of gene therapy. Therefore we **recommend** that the proposed supervisory body should be non-statutory and, lest it be thought that the body would not be sufficiently independent of medical research interests, should be funded by, and be under the aegis of, the Department of Health.

7.12. At first, and probably for several years, gene therapy will be applicable to a small number of uncommon disorders and be confined to a few patients. As with other new specialised medical interventions we **recommend** that it be confined to a small number of centres whilst experience is gained.

8 Summary of Main Conclusions and Recommendations

(References in square brackets are to paragraphs in the Report)

8.1. The **Committee on the Ethics of Gene Therapy,** a non-statutory body, was set up by the Government on 28 November 1989 with the following terms of reference:

> "To draw up ethical guidance for the medical profession on treatment of genetic disorders in adults and children by genetic modification of human body cells; to invite and consider proposals from doctors wishing to use such treatment on individual patients; and to provide advice to United Kingdom Health Ministers on scientific and medical developments which bear on the safety and efficacy of human gene modification".

8.2. Although there are effective treatments for some genetic disorders conventional treatments for most of them are inadequate and, for many, are limited to the relief of symptoms. Gene therapy offers for the first time the prospect of effective treatment and cure in many genetic disorders [1.8, 1.9, 2.13–2.15].

Ethical Basis

8.3. Before gene therapy is introduced into medical practice it must be ethically acceptable. To find an ethical position which would command acceptance for the forseeable future we have consulted widely. We have also taken careful notice of the treatment of these matters in other countries of similar cultural heritage. Unsurprisingly, the same questions have been discussed elsewhere, with a consistency in approach and underlying ethical conviction which have made our task easier [1.10–1.12, 3.1–3.7]. Our discussions and enquiries confirmed our tentative view that gene therapy should initially be regarded as research involving human subjects. It should therefore conform with accepted ethical codes whose purposes, together with the means of giving them force, are to:

(a) facilitate justifiable advancement of biomedical knowledge;
(b) maintain ethical standards of practice;
(c) protect the subjects of research from harm;
(d) preserve subjects' rights and liberties; and
(e) provide reassurance to the public, to the professions and to Parliament that these are being done.

We consider what in gene therapy research is justifiable, and the conditions that should be met for such research to be ethical and seen to be so [3.8–3.13].

Somatic Cell Gene Therapy

8.4. The purpose of somatic cell gene therapy in an individual patient is to alleviate disease in that individual, and that individual alone. We conclude that the development and introduction of safe and effective means of gene modification for this purpose is a proper goal for medical science. We therefore **recommend** that the necessary research should continue [4.1, 7.1].

8.5. Somatic cell gene therapy may hold great potential benefit for some patients; but it may also carry risks. To ensure that the benefits are assessed and the risks are identified as expeditiously as possible, we **recommend** that somatic cell gene therapy should, for the present, be conducted according to the discipline of research and governed by the exacting requirements which already apply in the United Kingdom to research involving human subjects [4.1–4.2, 4.5–4.16, 7.1, 7.3].

8.6. The first candidates for somatic cell gene therapy should be patients who are suffering from a disorder which is life threatening, or causes serious handicap, and for which treatment is unavailable or unsatisfactory, but which has not already progressed so far as to reduce significantly the potential for benefit. Some genetic disorders lead to irreversible and cumulative effects from early childhood, and even before birth. In such instances therapy must be given correspondingly early in life [4.3–4.4, 7.4].

8.7. We are firmly of the view that gene therapy should be directed to alleviating disease in individual patients, although wider application may soon call for attention. In the current state of knowledge any attempt to change human traits not associated with disease would not be acceptable [4.22, 7.5].

8.8. Somatic cell gene therapy will be a new kind of treatment, but it does not represent a major departure from established medical practice, nor does it, in our view, pose new ethical challenges. However, because of the special qualities of an individual's genetic make-up and the complex nature of genetic disorders, familiar issues assume greater prominence. They are:

(a) questions of safety, which are heightened by the possibility of inadvertent and unpredictable consequences of gene therapy to the patient, and the possible long term consequences [4.6, 4.7];

(b) the need for long term surveillance and follow-up [4.9];

(c) the matter of consent, especially in view of (a) above [4.11–4.13];

(d) the probability that children will be among the first candidates for therapy [4.13];

(e) confidentiality, and any necessary disclosure in respect of genetic information which may be important to kindred [4.14–4.16].

Germ Line Gene Therapy

8.9. The purpose of gene modification of sperm or ova or cells that produce them would be to prevent the transmission of defective genes to subsequent generations. Gene modification at an early stage of embryonic development might be a way of correcting gene defects in both the germ line and somatic cells. However, we have concluded that there is insufficient knowledge to evaluate the risks to future generations. We **recommend,** therefore, that gene modification of the germ line should not yet be attempted [5.1, 5.2, 7.2].

Supervision of Gene Therapy

8.10. A decision on whether gene therapy research on human subjects should proceed must depend on the careful assessment of the scientific merits of the proposal, the competence of those wishing to carry it out and the potential benefits and risks. This assessment should include a critical examination of arrangements for the conduct of therapy and subsequent monitoring. It will necessarily call upon an uncommon degree and range of scientific and medical expertise. Similar expertise is required to provide advice to Ministers. No existing body is constituted for this task. Accordingly we **recommend** that a supervisory body with the necessary collective expertise, experience and authority be set up, having the responsibility for making such assessments in conjunction with local research ethics committees (LRECs) [4.5–4.10, 6.1–6.4, 7.6–7.8]. We **recommend** that this supervisory body should have a responsibility for:

(1) advising on the content of proposals, including the details of protocols, for therapeutic research in somatic cell gene modification;

(2) advising on the design and conduct of the research;

(3) advising on the facilities and service arrangements necessary for the proper conduct of the research;

(4) advising on the arrangements necessary for the long term surveillance and follow-up of treated patients;

(5) receiving proposals from doctors who wish to conduct gene therapy in individual patients and making an assessment of:

  (a) the clinical status of the patient;

  (b) the scientific quality of the proposal, with particular regard to the technical competence and scientific requirements for achieving therapy effectively and safely;

  (c) whether the clinical course of the particular disorder is known sufficiently well
  —for sound information, counselling and advice to be given to the patient or those acting on behalf of the patient
  —for the outcomes of therapy to be assessable;

  (d) the potential benefits and risks for the patient;

  (e) the ethical acceptability of the proposal.

In the light of this assessment the expert supervisory body should make a recommendation on whether the proposal should be approved, and if so on what, if any, conditions. The supervisory body should also have a responsibility for:

(6) acting in co-ordination with LRECs;

(7) acting as a repository of up-to-date information on research in gene therapy internationally;

(8) setting up and maintaining a confidential register of patients who have been the subjects of gene therapy;

(9) oversight and monitoring of the research;

(10) providing advice to Health Ministers in the United Kingdom, on scientific and medical developments which bear on the safety and efficacy of human gene modification.

8.11. We **recommend** that any proposal for gene therapy should be approved by the new body as well as by a properly constituted LREC, and that anyone wishing to conduct such research should submit proposals simultaneously to both [6.3–6.4, 7.7–7.8].

8.12. We **recommend** that the attention of the Advisory Committee on Gene Manipulation (ACGM) be drawn to our report [7.9].

Control and discipline

8.13. We also **recommend** that there should be an effective means of control and discipline. If it comes to the attention of a LREC that research is being carried out which it has not been asked to consider, or which it has considered but its recommendations have been ignored, then that ethics committee should bring the matter to the attention of its appointing authority, the relevant NHS body, and to the appropriate professional body; and the supervisory body should bring it to the attention of Ministers [7.10].

8.14. The arrangements that we recommend are, we submit, adequate to provide the safeguards necessary to ensure ethical practice when gene therapy is proposed. They should also be flexible enough to adapt to foreseeable changes in research and clinical practice in the field of gene therapy. Therefore, we **recommend** that the proposed supervisory body should be non-statutory and, lest it be thought that the body would not be sufficiently independent of medical research interests, we **recommend** that it should be funded by, and be under the aegis of, the Department of Health [7.11].

8.15. As with other very specialised medical interventions we **recommend** that gene therapy be confined to a small number of centres whilst experience is gained [7.12].

Annex A Letters inviting the submission of evidence to the Committee

Committee on the Ethics of Gene Therapy

Room B1210 Alexander Fleming House
Elephant and Castle London SE1 6BY

Telephone 071-972 4194
FAX 071-407 2918

Chairman
Sir Cecil Clothier KCB QC

To: Individuals and Organisations

Your reference

Our reference FPS 15/51/3

Date 12 June 1990

Committee on the Ethics of Gene Therapy

I am writing to invite you to submit written evidence to the Committee which the Health Ministers in the United Kingdom have set up under the chairmanship of Sir Cecil Clothier KCB QC to examine the implications of the prospect of treating certain conditions by gene therapy. Its terms of reference are:

> To draw up ethical guidance for the medical profession on treatment of genetic disorders in adults and children by genetic modification of human body cells; to invite and give ethical consideration to proposals from doctors wishing to use such treatment on individual patients and to provide advice to the United Kingdom Health Ministers on scientific and medical developments which have a bearing on the safety and efficacy of human gene modification.

Views on any matters relevant to these terms of reference will be welcome.

Unless you specify that you wish the response you make to be in confidence, a stipulation which we would of course adhere to strictly, your evidence will be made public after the Committee has completed its work in the sense that it will be placed in the Libraries of both Houses of Parliament and the Library of the Department of Health.

A list of those bodies which are being invited to give evidence is attached. The Committee would, however, be glad to hear from anyone with an interest in its work. I enclose a copy of the Press Release announcing the setting-up of the Committee, which contains a list of members and some further information which may be helpful.

Responses should be sent to me by 7 September at this address. If you think you may have problems meeting this deadline, please let me know.

Yours sincerely,

Mrs Sue White

Administrative Secretary to
the Committee

Enclosures are not reproduced in the Report of the Committee on the Ethics of Gene Therapy.

To: Editors of Professional Journals

Your reference
Our reference FPS 15/51/3
Date 6 June 1990

Dear Editor,

Gene Therapy

Readers will be aware that in November 1989 the United Kingdom Health Ministers announced the establishment of a Committee with the following terms of reference:

> " To draw up ethical guidance for the medical profession on treatment of genetic disorders in adults and children by genetic modification of human body cells; to invite and give ethical consideration to proposals from doctors wishing to use such treatment on individual patients and to provide advice to the United Kingdom Health Ministers on scientific and medical developments which have a bearing on the safety and efficacy of human gene modification."

The Committee is at present at the stage of collecting evidence which it will consider in the course of drawing up guidance, and would welcome views on any matters relevant to these terms of reference from individuals or organisations who have not yet had an opportunity to contribute.

Any such responses should be sent to:

Mrs Sue White

Administrative Secretary
Committee on the Ethics of Gene Therapy
Room B1210
Alexander Fleming House
Elephant and Castle
London SE1 6BY

Tel. 071-407 5522 Ext. 6980

Yours sincerely,

Sue White

Administrative Secretary
Committee on the Ethics of
Gene Therapy

To: Chairmen of Local Research Ethics Committees

6 June 1990

Dear Chairman

Gene Therapy

In November 1989 the United Kingdom Health Ministers announced the establishment of a Committee with the following terms of reference:

> "To draw up ethical guidance for the medical profession on treatment of genetic disorders in adults and children by genetic modification of human body cells; to invite and give ethical consideration to proposals from doctors wishing to use such treatment on individual patients and to provide advice to the United Kingdom Health Ministers on scientific and medical developments which have a bearing on the safety and efficacy of human gene modification."

The Committee is at present at the stage of collecting evidence which it will consider in the course of drawing up guidance. The crucial role played by ethics committees in considering these important issues is recognised, and the Committee therefore invites LRECs to submit comments on any matters relevant to these terms of reference. It would also welcome views on the practical matter of the potential interaction between LRECs and the Committee.

Comments should be sent to:

Mrs Sue White

Administrative Secretary
Committee on the Ethics of Gene Therapy
Room B1210
Alexander Fleming House
Elephant and Castle
London SE1 6BY

It would be helpful if your responses could reach me by Monday 23 July, if possible.

Yours sincerely,

Sue White

Administrative Secretary
Committee on the Ethics of
Gene Therapy

Annex B List of organisations and individuals from whom submissions were received

Association of Community Health Councils
Association of Medical Research Charities
Association of Scottish Local Health Councils
Board of Deputies of British Jews
Board of Social Responsibility of the Church of England
British Medical Association
British Psychological Society
Chief Rabbi
Christian Medical Fellowship
Clinical Genetics Society
Clinical Molecular Genetics Society
Consumers for Ethics in Research (CERES)
Council of Mosques: United Kingdom and Eire
Division of Social Responsibility—Methodist Church
Doctors who Respect Human Life
Feminists Against Eugenics
Free Church Federal Council
General Medical Council
Genetic Interest Group
Guild of Catholic Doctors
Health Visitors Association
Joint Medical Genetics Co-ordinating Committee
Local Research Ethics Committees (see below)
Medical Research Council
Medical Women's Federation
National Council of Women of Great Britain
Public Health Laboratory Service
Royal College of General Practitioners
Royal College of Midwives
Royal College of Nursing
Royal College of Obstetricians & Gynaecologists
Royal College of Physicians of Edinburgh
Royal College of Physicians of London
Royal College of Psychiatrists
Royal College of Surgeons of Edinburgh
Royal Society
The Board of Mission
United Free Church of Scotland
United Kingdom Central Council for Nursing, Midwifery, and Health Visiting
Union of Liberal and Progressive Synagogues
Church in Wales

Responses from local research ethics committees

Airdale Health Authority
Barnet Health Authority
Blackburn, Hyndburn and Ribble Health Authority
Bristol and Weston Health Authority
Bromsgrove and Redditch Health Authority
Central Birmingham Health Authority
Cheltenham and District Health Authority
Chichester Health Authority
Coventry and North Warwickshire Health Authority
Darlington Health Authority
East Birmingham Hospital

East Hertfordshire Health Authority
East Surrey Health Authority
Great Yarmouth and Waveney Health Authority
Hampstead Health Authority
Herefordshire Health Authority
Hillingdon Health Authority
Kent and Canterbury Hospital
Kidderminster Health Authority
Lancaster Health Authority
Leicestershire Health Authority
Liverpool Health Authority
Mid Staffordshire Health Authority
North Hertfordshire Health Authority
Northallerton Health Authority
Northumberland Health Authority
Norwich Health Authority
Nottingham City Hospitals
Nottingham Health Authority (Queen's Medical Centre)
Nottingham Medical School
Oxford Psychiatric Research Ethics Committee
Oxfordshire Health Authority
Peterborough Health Authority
Rotherham Health Authority
Rugby Health Authority
Sheffield Health Authority
South Cumbria Health Authority
South Derbyshire Health Authority
South East Staffordshire Health Authority
South Manchester Health Authority
South Tyneside Health Authority
South Warwickshire Health Authority
South West Hertfordshire Health Authority
Southampton and South West Hampshire Health Authority
Tower Hamlets Health Authority
Walsall Health Authority
West Berkshire Health Authority
West Birmingham Health Authority
West Cumbria Health Authority
West Dorset Health Authority
West Lambeth Health Authority
Worthing Health Authority

Further Reading

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Glossary

(Terms in italics appear as items in the Glossary)

Allele (allelomorph)

Any of the alternative *genes* which may occupy corresponding positions (*loci*) on each *chromosome* of a pair. A *mutation*, such as one which may be responsible for genetic disease, is an allele.

Amino acid

A simple compound, one of 20 from a selection of which all *proteins* are made. Proteins have different characteristics because in each of their constituent chains (*polypeptides*) particular amino acids are arranged in a particular order. *Genes* specify this arrangement.

Base

In the context of genetics a *nucleotide*, one of the four compounds, cytosine, adenine, thymine and guanine (often abbreviated respectively to C, A, T and G). They are the components of *DNA* which enable it to carry genetic information. The four bases provide a chemical alphabet, a combination of three of which codes each *amino acid* constituent of a *polypeptide* chain of a *protein*. The order of such combinations within a particular region of DNA specifies the order of amino acids in the corresponding polypeptide. The sequence of bases specifying a complete polypeptide is a *gene*.

Body cell (*somatic cell*)

Any *cell* of the body except a *germ line cell*. Changes in body cells, notably changes in their genetic make-up, affect only the individual who possesses them, not individuals of succeeding generations.

Cell (see also: *body cell, germ line cell, somatic cell*)

The smallest unit of living organisms which, given the right conditions, can survive independently and reproduce itself. Normally each cell has one *nucleus*. It has been estimated that the body of a human adult comprises 50 million million cells.

Chromosomes

Microscopically characteristic bundles which carry the *DNA* contained in the *nucleus* of a *cell*, and the vehicles in which the DNA is carried during reproduction. Each chromosome contains a very long double strand of DNA, bearing thousands of *genes* in a linear array. Chromosomes are present in pairs, the *diploid* state, in *body cells*, but only one of each pair is present in *gametes*, the *haploid* state. In human beings there are normally 46 chromosomes. 44 are arranged, and numbered in order of decreasing size, as 22 matching (homologous) pairs called autosomes. The two remaining chromosomes are sex chromosomes, in females XX and in males XY. One of each pair of the autosomes and one X are of maternal origin, and the other 23 are of paternal origin.

Cystic fibrosis (see also: *genetic disease or disorder*)

In the United Kingdom the most common single gene disorder, affecting about one in 2,000 children. The genetic defect results in the production of abnormally thick mucus. The mucus obstructs the airways of the lung and leads to recurrent respiratory infection and lung damage, and it obstructs glands of the intestine and leads to impaired digestion and absorption of food. The disorder requires lifelong treatment to combat infection and to enhance nutrition. Genetic inheritance is *recessive*.

Congenital

Present at birth.

Deoxyribose

A constituent of *DNA* (*deoxyribonucleic acid*)

Differentiation

The process of development whereby unspecialised *cells* or *tissues* become specialised for their particular tasks.

Diploid (see *chromosomes, mitosis*)

DNA (deoxyribonucleic acid)

The chemical substance of which a *gene* is made and which encodes genetic information.

Dominant (see also: *allele, recessive, X-linked*)

The state of affairs when one *allele* overrides the outward expression of another. A dominant *gene* exercises the same outward effect when inherited from only one parent as when inherited from both. Genes that make their effects apparent only when inherited from both parents are said to be *recessive.*

Down's syndrome

A *genetic disorder* in which characteristic physical features are accompanied by learning difficulty. The disorder is the consequence of a chromosomal abnormality in which, most commonly, there is an additional *chromosome* (that numbered 21).

Duchenne muscular dystrophy (see also: *genetic disease or disorder*)

A single gene disorder which affects about one in 5,000 boys. The condition produces progressive weakness of proximal muscles, beginning in early childhood. Most affected children, all of whom are boys, become chairbound before adulthood. Inheritance is *X-linked,* i.e. it is transmitted from *heterozygous* females, who are unaffected and are described as carriers, to sons who are affected, and to daughters who, like their mothers, are unaffected carriers.

Enzyme

A *protein* which catalyses one of the body's many chemical reactions, which together constitute metabolism—the processes that enable continued functioning and growth. A deficit in the production of an enzyme or its working may be caused by a *mutation,* resulting in an inherited disorder of metabolism.

Expressed (of a *gene*: see *gene expression*)

Gamete (see also: *chromosomes*)

A reproductive *cell*: sperm in males, ova in females. It carries inherited characteristics from parent to offspring.

Gene

An element of the *genome* which may be responsible for an inherited character difference. A sequence of *bases* in *DNA* which codes for one *polypeptide.*

Gene expression

The production by a *cell* of the *polypeptide* for which the specific gene codes.

Gene pair (see also: *chromosomes*)
Corresponding genes in each of a pair of matching (homologous) *chromosomes*.

Gene pool
A term used to describe all the genes at a given *locus* (or, sometimes, the genes at all *loci*) in the population.

Genetic disease or **disorder**
Afflictions which are the result of defects in the genetic endowment of an individual. They may be the direct consequences of defects in single *genes* (*mutations*); or in whole *chromosomes*, parts of which may be lost, duplicated or misplaced; or from the interaction of multiple genes and external factors in fetal development. Later in life such interactions seem to be the basis of many of the common serious disorders, such as heart disease, diabetes, and cancer, although these are not usually thought of as genetic disorders.

Gene therapy
Used without qualification means the genetic modification of *body cells* of an individual patient, directed to alleviating disease in that patient.

Genome
A term variously used to describe the genetic complement of an individual, or of a species, and characteristic of that individual or species.

Germ line cells (see also: *gamete, chromosomes*)
Those *cells* which are set apart early in embryonic life to become *gametes*, cells of reproduction; sperm in males, ova in females.

Haemoglobin
Red, oxygen carrying pigment of the blood. Haemoglobin incorporates two pairs of *polypeptides* called globins. Various gene *mutations* which affect the kinds of globin made, or their amounts, can result in diseases called the haemoglobinopathies, notably the *thalassaemias* and *sickle cell disease*.

Haemophilia (see also: *genetic disease or disorder*)
A single gene disorder, which affects about 1 in 10000 males, in which there is defective production of a *protein* that is necessary for blood clotting and thereby prevents excessive bleeding. Its inheritance is *X-linked* (see also: *Duchenne muscular dystrophy*).

Haploid (see *chromosomes, meiosis*)

Heterozygote
An organism is described as a heterozygote when it has inherited unlike *alleles* of a specific *gene pair* from its parents. If the alleles are the same the organism is *homozygous* for that gene.

Homozygote (see *heterozygote*)

Hormone
A chemical messenger which circulates in the blood, eg insulin, sex hormones.

Huntington's disease (see also: *genetic disease or disorder*)

A single gene disorder which affects about 1 in 2000 people and in which, during adult life, there is worsening involuntary movement, accompanied by progressive dementia. It is inherited as a *dominant* characteristic.

In vitro (see also: *in vivo*)

Describes a biological process conducted outside the body of the living organism. Literally " in the glass ", as in a test-tube.

In vivo (see also: *in vitro*)

Describes a biological process conducted in the living organism.

Locus (pl. loci)

In genetics the place on a *chromosome* which is occupied by a *gene*.

Malformation

A fault in the primary development of an *organ* or *tissue*, and therefore present at birth.

Meiosis

The form of cell division by which *gametes* are formed. It is described as a reduction division, the gametes each receiving only one of each pair of *chromosomes*, the *haploid* state.

Mitosis

Cell division of *somatic cells*. Each daughter cell receives both *chromosomes* of each pair, the *diploid* state.

Molecular biology

The study of *proteins* and *nucleic acids*, substances that make up the living world, their structures and their relationship to biochemical activity; and the substances that are the repositories of genetic information and the agencies for its communication from one generation to the next.

Mutation

A molecular event in which *DNA* is altered with genetic consequences. A *gene* which has undergone mutation is called a mutant; so also is an organism in which the mutant gene is *expressed*.

Nucleotide (see *base*)

Nucleus (see also: *cell*)

The place in a *cell* where *chromosomes* lodge.

Organ (see *tissue*)

Polypeptide

The chain of *amino acids* which comprises part or all of a *protein*.

Protein

The complex structure made from one or more *polypeptide* chains. Proteins are essential constituents of the body. They form the structural materials of muscles, *tissues*, *organs* and are regulators of function, as *enzymes* and some *hormones*.

Recessive (see also: *allele, dominant, X-linked*)

A *gene* that exercises little or no outward effect unless it is present in both of a pair of *chromosomes,* and therefore has been inherited from both parents, is said to be recessive.

Replication

The process whereby *DNA* makes copies of itself when a *cell* divides. The two strands of the DNA molecule unwind, and each strand directs the synthesis of a new strand complementary to itself (and identical to its former partner).

RNA (ribonucleic acid)

Forms of nucleic acid which are concerned with the synthesis of *protein.* Messenger RNA is the means whereby the recipe for a *polypeptide* encoded in *DNA* which is contained in the *nucleus* of a *cell,* is transcribed and carried to the place in the cell where proteins are synthesised (the cytoplasm). The transcribed recipe then guides the assembly of the corresponding protein, a process called translation.

Ribose

A constituent of *RNA (ribonucleic acid)*

Sickle cell disease (see also: *genetic disease or disorder, haemoglobin*)

A single gene disorder caused by an altered *polypeptide* in the globin of *haemoglobin.* It was the first disorder in which a *mutation* in a structural *gene* was shown to produce an altered *amino acid* sequence. Inheritance is autosomal *recessive.* In *homozygotes* there is severe chronic anaemia, episodes of painful infarction (*tissue* death due to obstruction of the blood supply) especially of lungs, spleen and bones, and proneness to infection.

Somatic cell (see *body cell*)

Stem cell

A *cell* that throughout life is able to produce all the cells within an *organ.* A change, whether accidental or engineered, in the genetic complement of a stem cell will be passed to its progeny, by *mitosis,* and may be expressed in them. Appropriate stem cells are therefore an obvious target in somatic cell *gene therapy.*

Thalassaemias (see also: *genetic disease or disorder, haemoglobin*)

A group of disorders in which there is reduced production of one or more of the globin chains which constitute normal *haemoglobin.* The imbalance of globin chains results in chronic anaemia, which is a common cause of premature death and much suffering. Inheritance of each of the many genes which may be responsible is recessive.

Tissue

A collection of *cells* specialised to perform a particular function. Tissues are usually composed of several cell types. *Organs,* eg heart, kidney are made up of such tissues.

Trait

A character difference for which a *gene* is responsible.

Virus

A tiny infectious organism, too small to reproduce outside a host *cell*. Viruses carry either *DNA* or *RNA*, surrounded by *protein*. Some cause disease, eg chicken pox, influenza. Some viruses, however, suitably modified, can be used in research as a means of delivering a *gene* into cells.

X-linked

Describes the form of inheritance of diseases for which the *gene* responsible is carried on the X *chromosome*.

Zygote

A fertilized ovum.

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